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Case Report

Late diagnosis of central nervous system involvement associated with lethal dissemination of *Strongyloides stercoralis* in an advanced HIV patient from Nigeria

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SUMMARY

Strongyloides stercoralis is a ubiquitous intestinal nematode, endemic in tropical and subtropical areas, with an unusual life cycle in which autoinfection can take place. In the immunosuppressed host, autoinfection is accelerated and larvae can spread in all organs, leading to hyperinfection syndrome or to disseminated disease. Strongyloidiasis is presently rare in Western Countries, often with delayed diagnosis due to a lack of clinical suspicion, nonspecific presentation, and low parasite intestinal output. Foreign HIV-infected patients from endemic areas are at increased risk of severe disease caused by this parasite. Here we report the case of a patient with disseminated lethal disease, whose disseminated state was missed 2 years prior to the current presentation. This emblematic case shows that intestinal parasitic infections, highly prevalent in Sub-Saharan Africa, Southeast Asia, and Latin America, are difficult to recognize but should be thoroughly investigated and excluded in high-risk patients, to prevent severe long-term lethal sequelae.

1. Introduction

Strongyloidiasis is an emerging global infection that is underestimated in many countries[1]. The nematode Strongyloides stercoralis, causative agent of strongyloidiasis, is an opportunistic intestinal threadworm parasite that infects man, cats, dogs and can be passed from man to dogs or cats or vice versa[1]. Ground soil is the primary source of the nematode, where it is found in two forms, the adult worm and the larva: filariform larvae produced by adults can penetrate the intact skin after contact with contaminated soil[1].

Strongyloidiasis is endemic in tropical, subtropical and temperate regions, affecting 30-100 million people overall[1]. Immunocompromised individuals, particularly HIV-infected people, are the most vulnerable population at risk for developing life-threatening clinical syndromes, such as Hyperinfection Syndrome (HS) and dissemination[2]. In these hosts, autoinfection is accelerated and larvae can reach different organs: when migration is confined to respiratory and gastrointestinal systems, the picture is known as HS; disseminated infection occurs when involvement of other organs is present, with mortality rates as high as 80%[1]. Here we report on a case of disseminated lethal disease whose disseminated state was missed 2 years in advance.

2. Case report

A 33-year-old Nigerian male, who had been living in Italy since 2003, was first hospitalized in February 2008 due to fever, multiple lung infiltrates, severe hepatic cholestasis, peripheral and bone marrow hypereosinophilia, and enlarged axillary lymph nodes (7 cm in diameter in the right axilla). An HIV infection (clade CRF02_AG) was diagnosed, with 210 000 copies/ml and 350 CD4 T cells/mm^3. Genotype resistance testing (GRT) showed the following pattern: I13 V, K20I, M36I, L63P, H69K, and L89 M. Furthermore, hypergammaglobulinemia and high-level peripheral Epstein–Barr virus (EBV) replication (1503 copies/ml) were detected, and a liver biopsy revealed high loads of both cytomegalovirus (CMV) DNA (3616 copies/μg) and EBV DNA (2072 copies/μg). During his hospitalization, eosinophil counts reached 600 cells/mm^3 (11.1%), rising to 1900 cells/mm^3 (19.4%) after 15 days. A chest computed tomography (CT) scan showed the presence of parenchymal thickening on the anterior segment of the right upper lobe, other circumscribed areas of thickening in the posterior segment of the same lobe, and the presence of lymph nodes in the axilla bilaterally. He was treated with clarithromycin, ceftriaxone, co-trimoxazole, meropenem, and antiretroviral therapy. A histological lymph node

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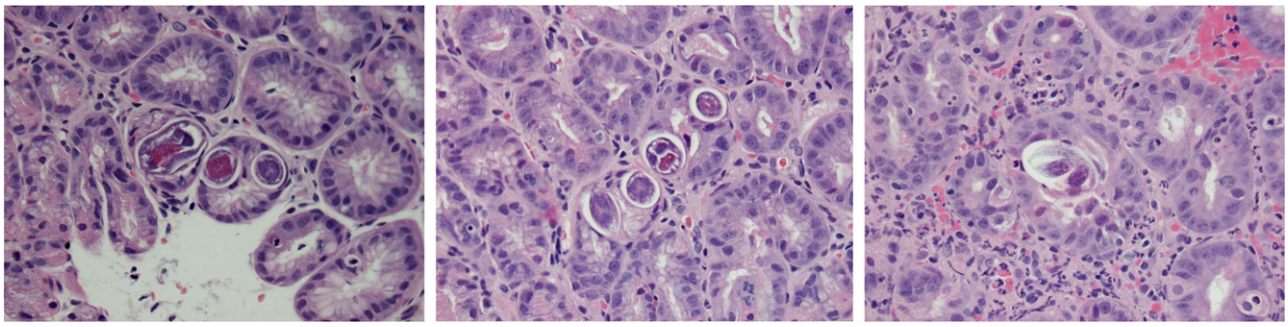

Figure 1. Detection of *Strongyloides stercoralis* in a gastric biopsy specimen: larvae and eggs in the gastric crypts; hematoxylin–eosin ×400.

examination revealed giant-cell granulomatous necrotizing lymphadenitis; PCR amplifications ruled out mycobacterial infections, human herpesvirus type 6 (HHV6), HHV8, varicella zoster virus (VZV), and Toxoplasma. Parasitological examinations of stools were repeatedly negative. Long-term corticosteroids, antiviral therapy (ganciclovir), and antiretroviral therapy with tenofovir/emtricitabine, darunavir, and ritonavir were rapidly beneficial. However the patient interrupted all treatments at 3 months after discharge and disappeared.

In August 2010, he was re-hospitalized due to fever and a lethargic state with nuchal rigidity. Early investigations showed remarkable elevations of C-reactive protein, fibrinogen, D-dimer, ammonium, transaminases, alkaline phosphatase, and gamma-glutamyl transpeptidase.

At this time, there was no evidence of peripheral eosinophilia. On admission, the CD4 T cell count was 105 cells/mm^3, HIV RNA was 2170 copies/ml, and a cerebrospinal fluid (CSF) examination revealed high polymorphonuclear cell counts (85%, >1000/ml), high glucose, and low protein levels (1.8 mg/dl). CSF culture grew *Enterococcus faecalis*, while blood and urine cultures were negative. Intestinal sub-occlusion ensued, with persistent stomach ache. An X-ray of the abdomen and CT scans were unremarkable. Upper gastrointestinal tract endoscopy showed diffuse and severe inflammatory lesions in the esophageal and gastric mucous membranes. Cytological examinations of esophageal specimens revealed the presence of fungal hyphae and spores consistent with *Candida albicans*, with a positive culture for *C. albicans* on mouth swabs. Histological evaluation of gastric biopsies disclosed the presence of *Strongyloides stercoralis* (Figure 1). Repeated stool examinations revealed rhabditiform larvae of *S. stercoralis*. Serological assays (Immunofluorescent assay test, IFAT) for specific antibodies were negative. High-level peripheral CMV replication (58 850 copies/ml) was detected. In spite of treatment with oral ivermectin (200 μg/kg of body weight daily), the patient died a few days later due to progressive encephalopathy. Permission was not granted for an autopsy.

3. Discussion

In HIV-infected patients, the prevalence of Strongyloides infections is higher than the general population[2]. A study in 2009 showed that in the African population rates of infection with Strongyloides may be as high as 12.6%, in comparison with 0.6% of HIV negative subjects[3]. In these patients, factors that determine the occurrence of dissemination of S. stercoralis are not fully known. A fine equilibrium between T helper (Th1) and T helper 2 (Th2) response may play a key role[2].

Immune responses elicited by nematode infection in normal subjects are Th2 type, with high levels of IL-3, IL-4, IL-5, IL-13, eosinophils and specific IgA2. It has been suggested that B lymphocytes are essential for the acquisition of resistance to larval S. stercoralis, together with eosinophils, that are believed to function as antigen presenting cells for the induction of the primary and secondary Th2 immune response to S. stercoralis[2]. During early phases of his disease, the patient experienced vague symptoms such as fever, nausea and weight loss, with laboratory findings of hypereosinophilia and increased serum IgE concentrations[4]. Progressive Strongyloidiasis has been associated with a high incidence of bacterial or yeast infections and sepsis with meningitis due to Enterococcus faecalis signaled clinical evolution in our case. The postulated mechanism in such cases is transmission of enteric bacteria through the bowel wall by invading filariform larvae[5]. Unfortunately, the disease is largely unrecognized both in the uncomplicated and in the complicated cases, mainly due to the low level of clinical suspicion and to the low sensitivity of diagnostic tools. Several diagnostic methods have been compared to detect the presence of S. stercoralis, including stool examination, stool culture on a blood agar plate, enzyme-linked immunosorbent assay (ELISA), serum indirect fluorescent antibody test, PCR and gastrointestinal aspirate or biopsy4. However, all these techniques, frequently not feasible, provide results with low sensitivity and specificity[4]. As the case reported shows, the major clinical problem often lies in timely and effective recognition and treatment of patients, especially if they are immunocompromised and from endemic areas. The present case clearly underline the need to suspect un underlying gastrointestinal helminthic disease when Enterococcal meningitis is diagnosed in an at-risk patient. In this case, neither Enterococcal meningitis, nor eosinophilia in the early stages helped to prevent this missed diagnosis, due to persistent lack of clinical suspicion. The concurrent findings of high-load CMV-DNA and EBV-DNA on liver biopsy specimens and severe lymphoadenopathies contributed to divert from the right diagnostic suspicion, together with repeatedly negative parasitological examination of stools, in spite of the suggestive geographical origin of our patient. As gastrointestinal and meningeal symptoms set the stage of his clinical picture at his second in-hospital presentation, histological diagnosis of strongyloidiasis came from gastric biopsies, performed due to persistent gastric pain and intestinal sub-occlusion. The examination of multiple sections revealed a patchy distribution of the parasite. Sequential stool examinations, on purpose requested, revealed rhabditiform larvae of S. stercoralis on multiple specimens. According to many authors, there is no general agreement on the optimal diagnostic strategy for Strongyloides stercoralis infection, as well as laboratory findings are usually nonspecific, the method of parasite detection in a single specimen has very low sensitivity1. ELISA tests for antibodies may provide a high sensitivity (83-93%) and specificity (95-98%), but the presence of antibodies does not distinguish between past and current infection[4]. The examination of gastrointestinal specimens for larvae has been shown to be the most sensitive diagnostic procedure for S. stercoralis, with a false-negative frequency less

than 10%[1]. In summary, our case raises important issues related to strongyloidiasis in HIV-infected subjects. Helminthic infections, in particular strongyloidiasis, should be suspected when unexplained pulmonary and/or gastrointestinal symptoms occur in immunocompromised patients from endemic areas. Given the increasing number of immunocompromised individuals worldwide and the greater diffusion of migration flows, clinicians need to realize that risk factors for this neglected helminthic disease should be considered early in the management of even in complex clinical pictures, as timely treatment of the parasite may lead to higher rates of successful resolution.

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Conflict of interest: The authors have no competing interests to declare.

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